

# Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IL05/000128

International filing date: 03 February 2005 (03.02.2005)

Document type: Certified copy of priority document

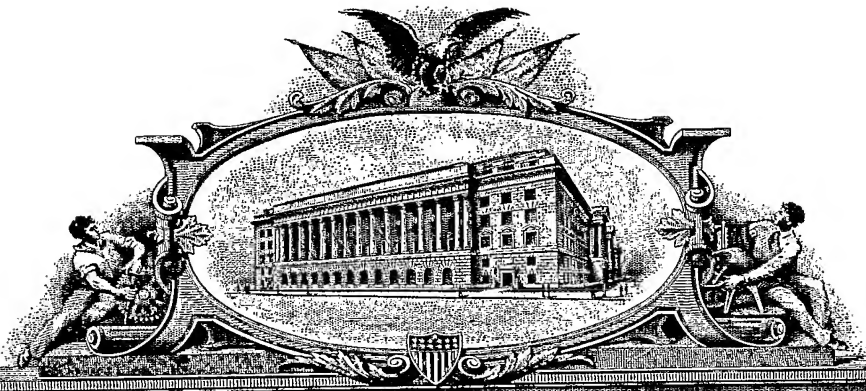
Document details: Country/Office: US  
Number: 60/541,923  
Filing date: 06 February 2004 (06.02.2004)

Date of receipt at the International Bureau: 22 March 2005 (22.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland  
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse



# THE UNITED STATES OF AMERICA

**TO ALL TO WHOM THESE PRESENTS SHALL COME:**

**UNITED STATES DEPARTMENT OF COMMERCE**

**United States Patent and Trademark Office**

**March 08, 2005**

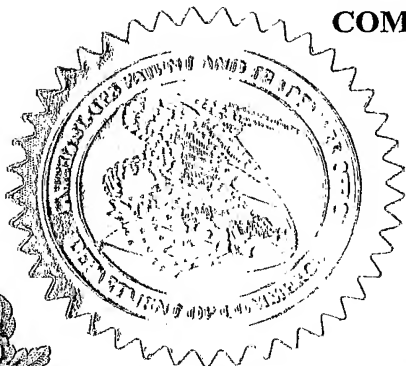
**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.**

**APPLICATION NUMBER: 60/541,923**

**FILING DATE: February 06, 2004**

1L/05/128

**By Authority of the  
COMMISSIONER OF PATENTS AND TRADEMARKS**



*Trudie Wallace*  
**TRUDIE WALLACE**

**Certifying Officer**

# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (b)(2).

Docket Number		27576		Type a plus sign (+) inside this box ->	+
INVENTOR(s) / APPLICANT(s)					
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)		
ADAM	Dan		Haifa, Israel		
TITLE OF THE INVENTION (280 characters max)					
LOCALIZED TREATMENT AND HYPERTHERMIA PRODUCTION BY MICROBUBBLES AND MICROBUBBLES-ENHANCED ULTRASOUND					
CORRESPONDENCE ADDRESS					
G. E. EHRLICH (1995) LTD. c/o ANTHONY CASTORINA 2001 JEFFERSON DAVIS HIGHWAY SUITE 207					
STATE	VIRGINIA	ZIP CODE	22202	COUNTRY	USA
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification	Number of Pages	10	<input checked="" type="checkbox"/> Applicant is entitled to Small Entity Status		
<input checked="" type="checkbox"/> Drawing(s)	Number of Sheets	7	<input checked="" type="checkbox"/> Other (specify)		
			3 Claims		
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)					
<input type="checkbox"/> A check or money order is enclosed to cover the filing fees			FILING FEE AMOUNT (\$)		\$ 80.-
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number:			50-1407		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.



No



Yes, the name of the US Government agency and the Government contract number are: \_\_\_\_\_

Respectfully submitted,

SIGNATURE

*Sol Sheinbein*

3 February 2004

Date

25,457

REGISTRATION NO.  
(if appropriate)

TYPED or PRINTED NAME SOL SHEINBEIN



Additional inventors are being named on separately numbered sheets attached hereto

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

## LOCALIZED TREATMENT AND HYPERTHERMIA PRODUCTION BY MICROBUBBLES AND MICROBUBBLES-ENHANCED ULTRASOUND

Inventor: Dan Adam

Rapid hyperthermia resulting in tissue ablation or necrosis has proven to be a useful therapeutic modality for cancerous tissue. Clinical application of high-intensity focused ultrasound (HIFU) is foreseen as the future non-invasive modality of choice, replacing the minimally invasive methods (RF ablation or Laser ablation). The ability to focus the ultrasound (US) energy at the specific location, with minimal absorption by neighboring tissue, by the tissue in between the transducer and that location, or by the tissue beyond that location – is the limiting factor of this technology.

At therapeutic intensities, the hyperthermia is often accompanied by bubble activity. In vitro and in vivo experiments alike have shown that under certain conditions bubble activity can give rise to a doubling of the heating rate (MRI-guided gas bubble enhanced ultrasound heating in in-vivo rabbit thigh, Sokka, S.D., King, R., Hynynen, K., Phys. Med. Biol. 48, pp. 223-241, 2003). Others have used cavitation suppression techniques to reduce the micro-bubble formation and make accurate ablation (Kentaro Tasaki, Takehide Asano, Kazuo Watanabe, Hiroshi Yamamoto, Division of Surgery, Chiba Cancer Center 666-2 Nitona, Chuo-ku, Chiba 260-8717 Japan). But more precisely, it was recently reported that a several times larger volume of tissue was coagulated with HIFU in a canine prostate with administration of Albunex Contrast Agent (CA) than without it. Kidneys were exposed to HIFU at 3.2 MHz in degassed saline, and when CA Optison was administered at a dose of 0.2 ml/kg, the temperature elevation induced by HIFU exposure was more than doubled. (The effect that tissue ultrasonic absorption will be doubled when contrast agent is added to the tissue at ~0.1 billion microbubbles/kg. was theoretically predicted, Umemura, Shin-ichiro Ken-ichi Kawabata, Kazuaki Sasaki, Central Research Laboratory, Hitachi Ltd., Kokubunji, Tokyo 185-8601, Japan).

The conflicting reports attest the difficulty and importance of harnessing the energy-concentrating effects of bubbles to do useful clinical work when exposed to ultrasound. The dominant heating mechanism depends on bubble size, medium shear viscosity number and frequency-dependent acoustic attenuation. The bubble size distribution, in turn, depends on insonation control parameters (acoustic pressure, pulse duration), medium properties (notably dissolved gas concentration) and bubble-destroying shape instabilities.

The current invention describes a method and a system that enables treatment by bubbles generated at a specific location and/or bubble-enhanced heating. It is based on the idea of initially generating bubbles using ultrasound radiation solely and how to generate it with minimal heat production, or with the addition of ultrasound contrast agent, at the location of interest, preferably, under the guidance and monitoring of an ultrasound imaging system. Additionally, ultrasound radiation of different waveform and/or focusing is then used to heat that same location. It includes the range of control parameters that assures that Ultrasound is more absorbed than scattered by the microbubbles by keeping them small (e.g. smaller than approximately 3 microns in radius).

The innovation is in the two-stage approach and how it is produced. Multiple high-power focused ultrasound transducers are used, housed within a structure that produces a common focus (which may be moved in order to re-focus or shift within the tissue). Each is powered by an amplifier, which is driven by a signal generator, usually tuned to a different frequency. This setup is designed to produce different wave-shapes, that usually contain high negative peaks and small positive peaks during the first stage – in order to produce microbubbles, then the wave-shape is modified, so as to produce heat while not allowing the microbubbles to grow in size, usually by containing positive peaks and only small negative peaks. An optional part of the invention is that the method and system may also include a control system, that measures the changes in tissue or the bubbles size, (e.g. by  $\frac{1}{2}$  harmonic imaging) and accordingly adjusts the wave-shape to include either more negative peaks, positive peaks or equal sized waves.

The system based on this method includes also an ultrasound imaging system, preferably sensitive to measure the existence of microbubbles in the tissue (e.g. by second harmonic imaging or by half harmonic imaging) and software that allows using the data from the imaging system as part of the control procedure. The system based on this method is meant to be placed extra-corporally, in close proximity to the organ to be treated, with ultrasound gel or water surrounding the ultrasound transducers and the space between it and the organ. The procedure itself is of short duration, with the first stage taking e.g. 10-30sec, and the second stage taking e.g. 30-90sec. The procedure must be repeated when larger regions need to be treated.

## **Summary of the invention and analysis of related art**

The current invention describes a method and a system that enables bubble-enhanced heating. It is based on the idea of initially generating bubbles using ultrasound radiation solely, or with the addition of ultrasound contrast agent, at the location of interest, preferably, under the guidance and monitoring of an ultrasound imaging system. Then ultrasound radiation is used to heat that same location. It includes the range of control parameters that assures that Ultrasound is more absorbed than scattered by the microbubbles by keeping them small (e.g. smaller than approximately 3 microns in radius).

The innovation is, in part, in the two-stage approach and how it is produced. Multiple high-power focused ultrasound transducers are used, housed within a structure that produces a common focus (which may be moved in order to re-focus or shift within the tissue). Each (transducer) is powered by an amplifier, which is driven by a signal generator, usually tuned to a different frequency. This setup is designed to produce different waveshapes, that usually contain high negative peaks and small positive peaks during the first stage – in order to produce microbubbles, then the waveshape is modified, so as to produce heat while not allowing the microbubbles to grow in size, usually by containing positive peaks and only small negative peaks. The method and system may also include a control system, that measures the changes in tissue or the bubbles size, and accordingly adjusts the waveshape to include either more negative peaks, positive peaks or equal sized waves.

The system based on this method includes also an ultrasound imaging system, preferably sensitive to measure the existence of microbubbles in the tissue (e.g. by second harmonic imaging or by half

harmonic imaging) and software that allows using the data from the imaging system as part of the control procedure.

The system based on this method is meant to be placed extra-corporally, in close proximity to the organ to be treated, with ultrasound gel or water surrounding the ultrasound transducers and the space between it and the organ. The procedure itself is of short duration, with the first stage taking 10-30sec, and the second stage taking 30-90sec. The procedure must be repeated when larger regions need to be treated.

The present invention finds uses in every one and all of, but not limited to, the medical applications and/or procedures mentioned and/or described in the following patent documents. Other uses are also envisaged.

List of Prior Art Patents (all of which are hereby incorporated by reference):

1.	5,209,720	Unger
2.	5,219,401	Cathignol et al
3.	5,316,000	Chapelon et al
4.	5,460,595	Hall et al
5.	5,558,092	Hunger et al
3.	5,601,526	Chapelon et al
7.	5,743,863	Chapelon
3.	5,817,048	Lawandy
3.	5,827,204	Grandia et al
0.	5,833,615	Wu et al
1.	5,882,302	Driscoll Jr. et al
2.	6,159,154	Takeuchi
3.	6,413,216	Cain et al
4.	6,425,867	Vaezy et al
5.	6,436,061	Costantino
6.	6,511,428	Azuma et al
7.	6,514,203	Bukshpan
8.	6,551,576	Unger et al
9.	6,576,220	Unger
10.	6,595,925	Oestensen et al
11.	6,626,855	Weng et al

The above patents relate generally to the use of ultrasound for imaging and/or hyperthermia treatment purposes. In most cases, the hyperthermia treatment is effected by High Intensity Focussed Ultrasound (HIFU) for purposes of destroying cancerous cells, but other treatments are also described. Examples of such other treatments include treating varicose veins (U.S. Patents 6,436,061 and 5,209,720); destroying blood clots (U.S. Patent 6,514,203); controlling internal bleeding (U.S. Patent 5,882,302); delivering substances to a treatment site (U.S. Patent 6,413,216); activating photosensitive therapeutic compounds at a treatment site (U.S. Patent 5,817,048); and shock-wave treatment (mentioned in U.S. Patent 5,316,000). U.S. Patent 6,511,428 discloses an intraluminal catheter which includes an ultrasound probe.

U.S. Patent 5,316,000 describes a probe for therapeutic treatments including a transducer of a composite construction, made of ceramic and polymer.

Many of the above-listed patents deal with the formation, and/or the composition, of microbubbles for enhancing the heating effect.

Two of these patents discuss the HIFU technique in considerable detail and various applications of the technique. One, namely U.S. Patent 6,425,867, is particularly directed to the HIFU technique for simultaneously imaging and heating by synchronizing the transducers such that noise in the imaging system rising from the heating transducer is shifted away from the treatment site. The other, U.S. Patent 6,626,855, is particularly directed to the HIFU technique for heat treatment by focussing the ultrasound to form an initial lesion at a distal (with respect to the ultrasound probe) boundary of the tissue to be destroyed, and controlling the ultrasound transmission to cause the lesion to progress towards the probe.

Some of the patents listed above utilize HIFU radiation having different frequency components. For example, U.S. Patent 5,827,204 first provides a low frequency ultrasound component for generating cavitation below threshold, and then adding a high-frequency ultrasound component to bring the ultrasound energy above the threshold in the treatment zone. U.S. Patent 5,743,863 utilizes HIFU of a wide band spectrum having multiple frequencies of the random or pseudorandom type to reduce or prevent cavitation. U.S. Patent 5,460,595 generates three resonant frequencies.

However, none of the above-listed patents appears to disclose the main concept of the new invention as briefly described above, namely the two-stage approach and particularly how it is produced. Thus, as briefly described above, the HIFU is generated by a plurality of transducers housed within a structure that produces a common focus, with each transducer powered by an amplifier driven by a signal generator tuned to a different frequency. As further briefly described, the set up is designed to produce different wave shapes that usually contain high negative peaks and small positive peaks during the first stage in order to produce microbubbles. In the second stage, the wave shapes are modified so as to produce heat while not allowing the microbubbles to grow in size, usually by having wave shapes containing positive peaks and only small negative peaks.

### **An example of the system configuration and parameters used:**

The power transducers are arranged as an array, designed so that their mechanical focus and their own focus combine at the same point in space. This point in space can be moved by either shift of the whole array, repositioning of individual transducers, or phase shift of the excitation pulse. The ultrasonic waves transmitted by different transducers are designed to produce by interference at the focal point specific waveforms (see for example Fig. 3) which are not produced at other locations. The waveforms can be modified to cause cavitation with no significant change in temperature, only increase of temperature with minimal cavitation or even suppression of cavitation, or a combination of these effects.



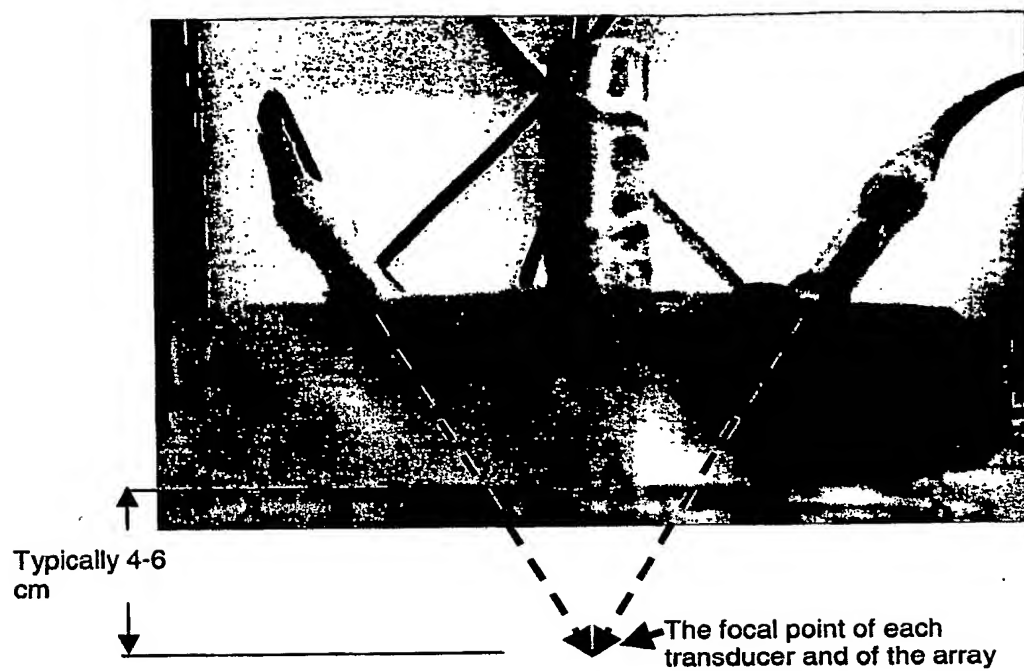


Fig. 1: The focal point of the array of ultrasound transducers is obtained at 6cm from the transducers holder, (in water, in gel at 5cm and in liver at 4cm).

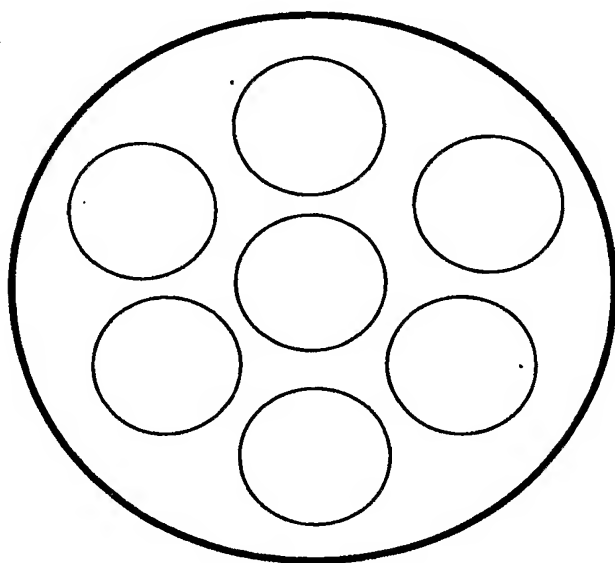


Fig. 2: One possible implementation of an array of transducers, when (6) cylindrical power transducers are used, all physically aimed at the same focal point. The 7<sup>th</sup> hole can be used for an imaging probe, connected to an imaging system, or for inserting thermocouples.

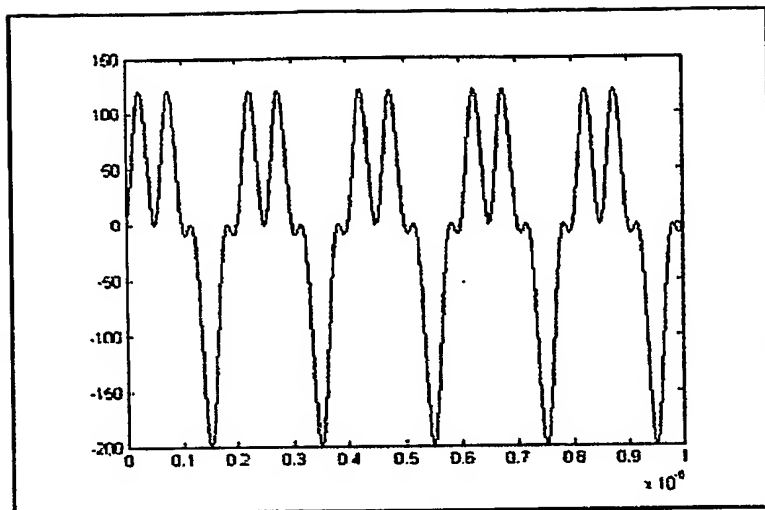
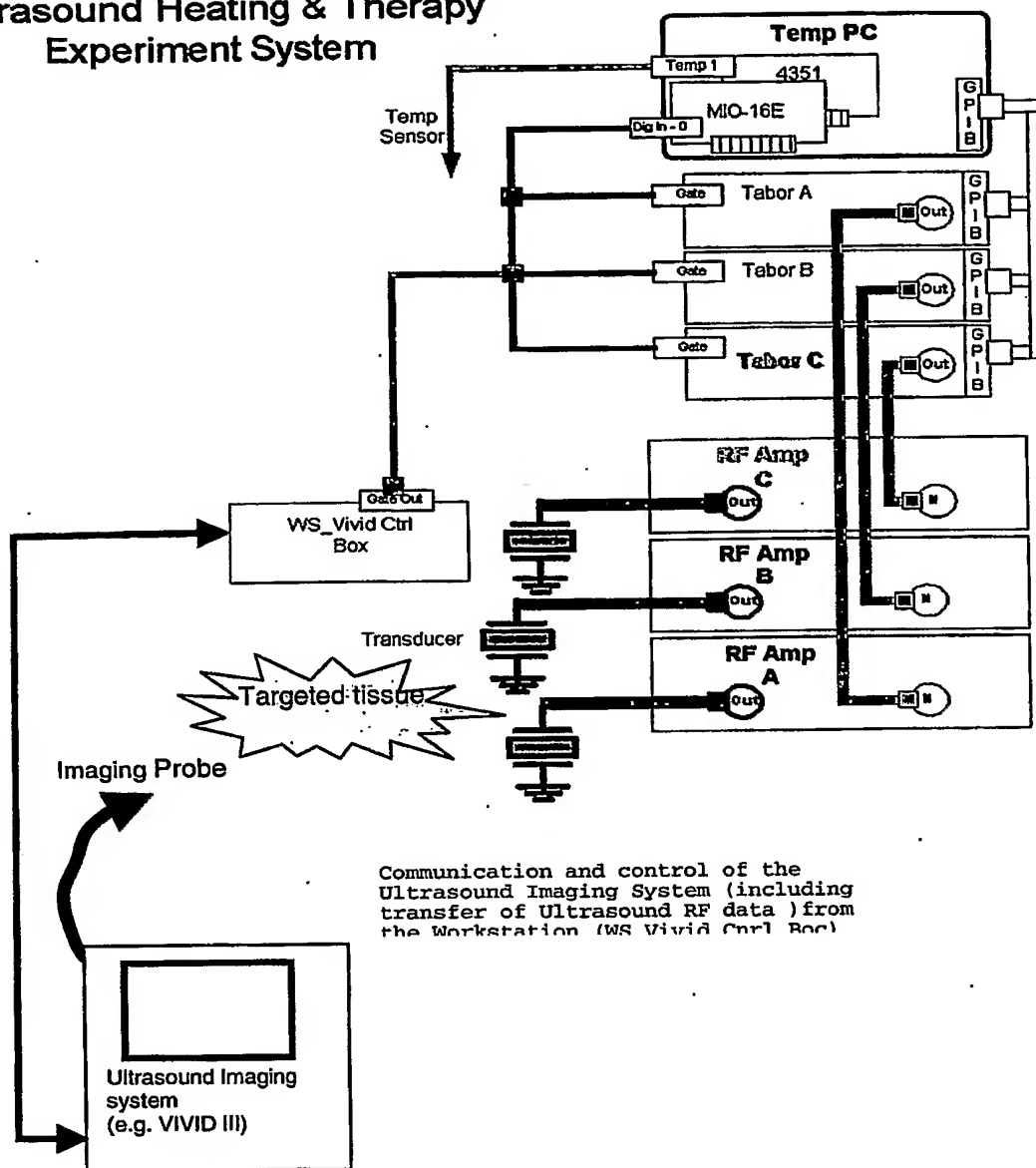


Fig. 3: An example of the cavitation waveform at the focus, produced by the array of transducers, operated under the conditions detailed in Table 1.

One possible implementation of the control and driving system is described in Fig. 4. The system includes arbitrary waveform signal generators (3 shown) connected to wide-band power amplifiers (3 shown, e.g. AR 150W 10kHz-100MHz), and through impedance matching to the transducers. The system is controlled by at least one workstation (PC) that controls the timing of activation of each arbitrary waveform signal generator, and its amplitude (by different cables and protocols. The workstation may also control a temperature measurement system, that measures and records temperatures (e.g. from thermocouples), and may modify the therapy according to the measured temperatures. Additionally or alternatively, an ultrasound system (imaging or non-imaging) may be used to view and monitor the region being treated (targeting), and/or may be used for aiming the focused beam to the targeted region. The ultrasound system may be used additionally or alternatively to monitor the generation of the microbubbles at the desired location, and control the system so that the amount of microbubbles will be as planned, and/or allow re-aligning of the beam to a different location. This step may be used for treatment, or a first stage where the second one causes increase of temperature, hyperthermia and/or ablation and destruction of the tissue. The ultrasound system may be used additionally or alternatively to monitor the treatment during the increased temperatures: the effects of the heating may be measured, the duration of the effect, the amount and the spatial distribution may be measured (by e.g. measuring the duration, amount and spatial distribution of microbubbles generated by the elevated temperatures, using the response at  $\frac{1}{2}$  harmonics of the transmitted frequency/ies). The ultrasound system may be controlled by the workstation.

# Ultrasound Heating & Therapy Experiment System



Communication and control of the  
Ultrasound Imaging System (including  
transfer of Ultrasound RF data )from  
the Workstation (WS Vivid Ctrl Box)

Fig. 4: a block diagram of the control and driving system. See text.

Table 1: The parameters of the signals during the cavitation stage – at Power Level 1

Transmission frequency	Voltage at the output of the Signal Generator ( $V_{pp}$ )	Voltage at the output of the Power Amplifier ( $V_{pp}$ )	Gain setting of the Power Amplifier	Phase of the signal
0.5MHz	180mV	165V	90%	0°
1.0MHz	100mV	80V	90%	90°
2.0MHz	100mV	37V	100%	270°

The control and driving system described in Fig. 4 may operate at different frequencies, phases, amplitudes (power) and durations, An example of parameters used for generation of cavitation – is given in Table 1.

### Typical results:

Effects of different power levels during cavitation: -

- power level 1 (red)
- power level 2 (green)
- power level 3 (blue)

The solid line is the mean of 5 experiments; the dashed lines are the variance range.

Results of a set of experiments is depicted in Fig. 5. Cavitation time: 30sec (nearly no heat is generated) + Heating time: 30sec (temperature rises to higher levels, depending on the amount of generated bubbles)

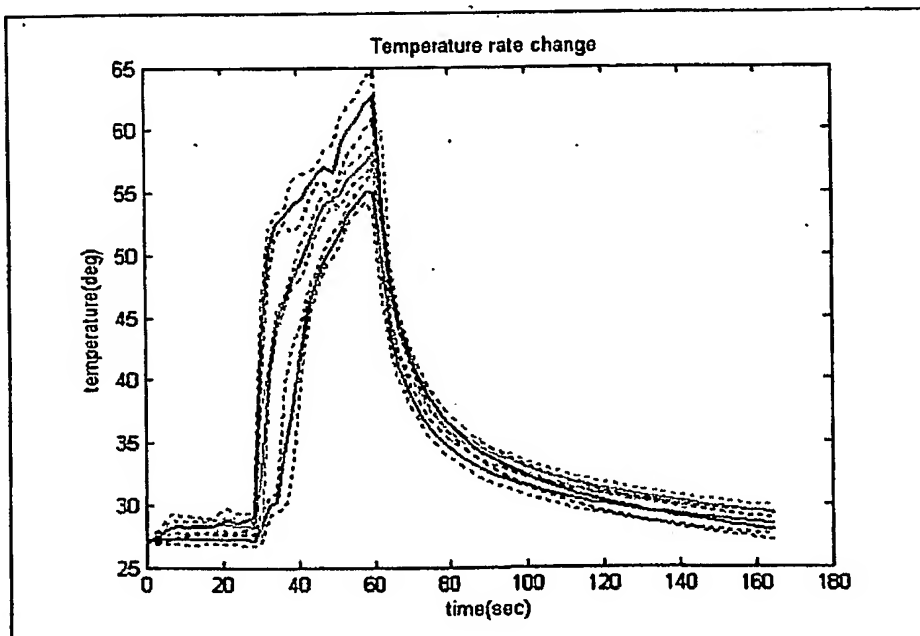


Fig. 5. Cavitation time: 30sec (nearly no heat is generated) + Heating time: 30sec (temperature rises to higher levels, depending on the amount of generated bubbles)

The results of an additional set of experiments are depicted in Fig. 6. Cavitation time: 30sec (nearly no heat is generated) + Heating time: 60sec ( the longer duration of heating causes some additional rise of temperature).

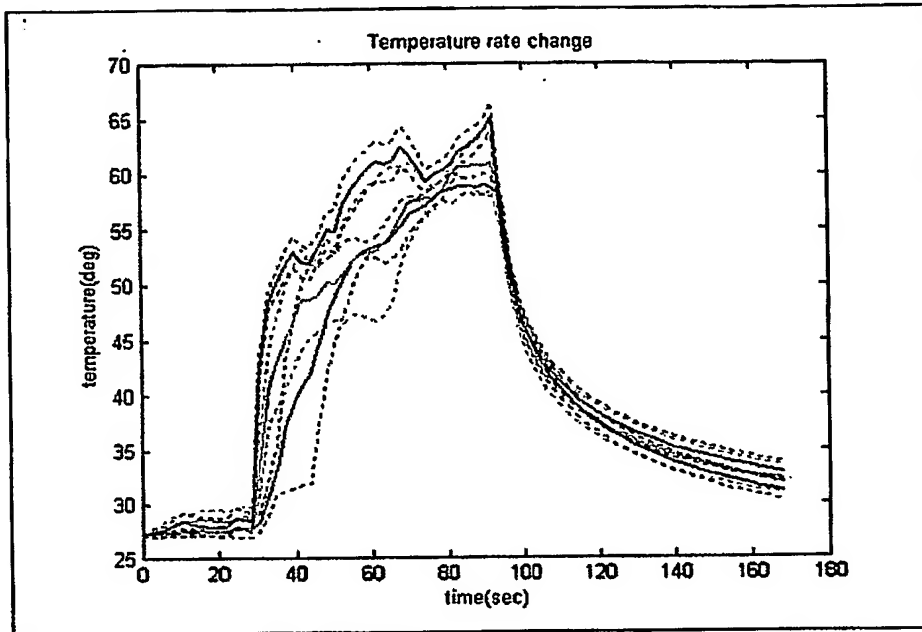


Fig. 6: Cavitation time: 30sec (nearly no heat is generated) + Heating time: 60sec ( the longer duration of heating causes some additional rise of temperature).

The Effects of different heating time durations are displayed in Figs. 7,8,9. ( 30sec (red line), and 60sec (blue line)) : Average temperature increase (results measured by thermocouples) at different power levels during cavitation (where none causes any significant increase of temperature).

Power level 1 (during cavitation):

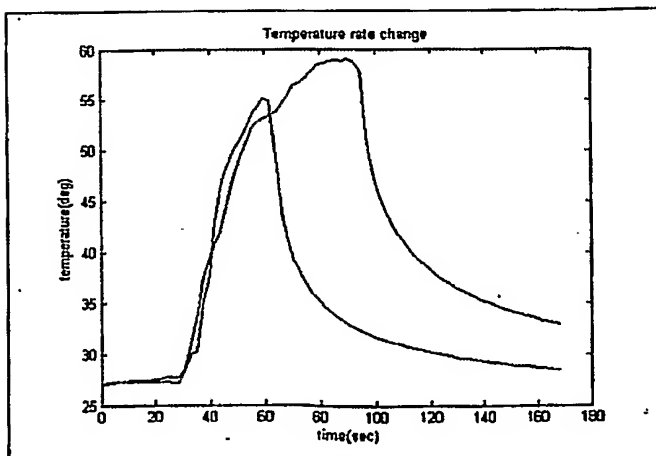


Fig 7: Average temperature increase (results measured by thermocouples) during different durations of heating (30sec and 60sec), when the cavitation phase was performed at the lowest power level (no significant increase of temperature is noticed during the cavitation phase).

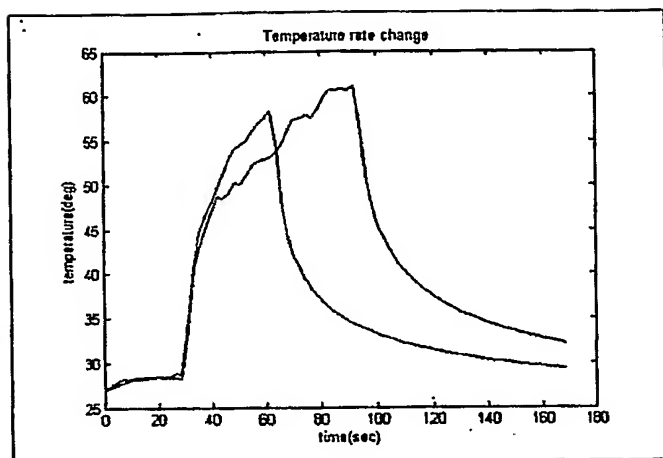


Fig 8: Average temperature increase (results measured by thermocouples) during different durations of heating (30sec and 60sec), when the cavitation phase was performed at midlevel power (no significant increase of temperature is noticed during the cavitation phase).

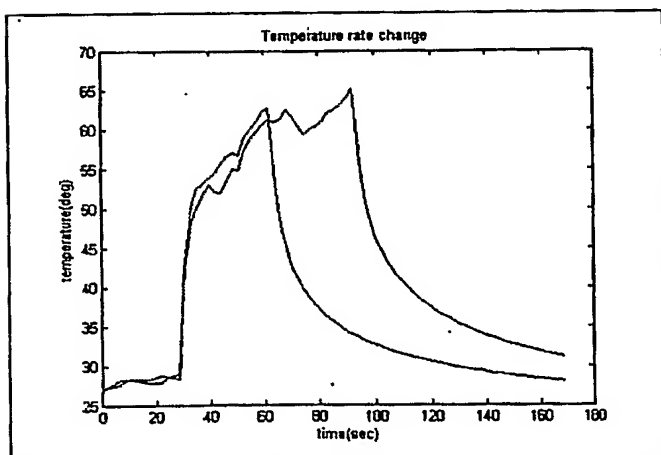


Fig 9: Average temperature increase (results measured by thermocouples) during different durations of heating (30sec and 60sec), when the cavitation phase was performed at high power level (no significant increase of temperature is noticed during the cavitation phase).

In experiments similar to the above, the maximal mean temperature reached after 60sec of heating only (with no cavitation) was 36.88 c°.

Ultrasound images of the heated area (Using the VIVID III imaging system):

B-mode images obtained before (0 sec) and after (30sec) production of cavitation at power level 2:

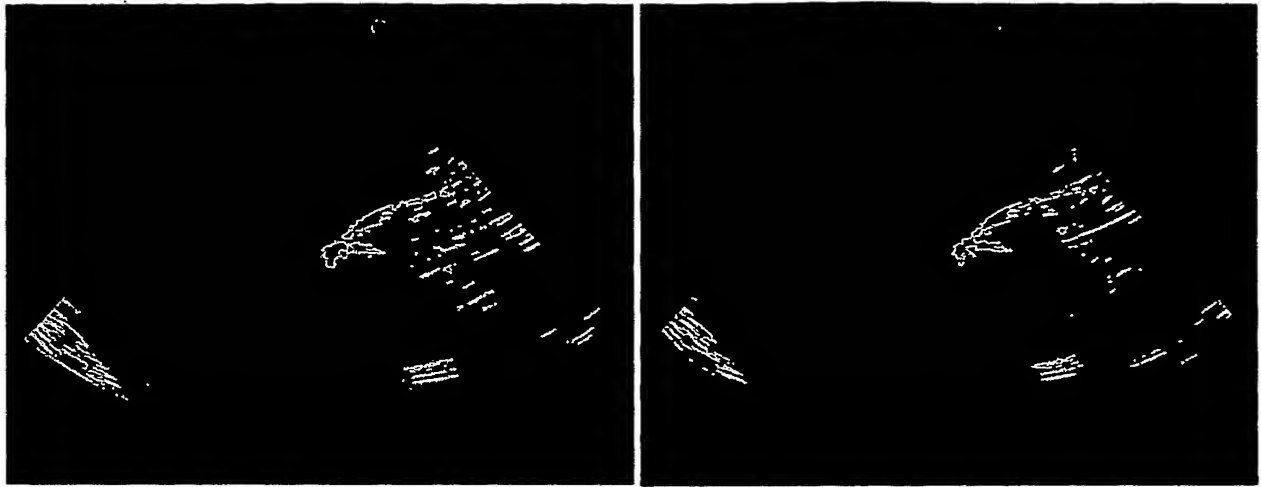


Fig. 10: B-mode images obtained before (0 sec) and after (30sec) production of cavitation at the midlevel power: No cavitation artifacts are seen – no increase echogenicity

### Typical Data Processing Scheme:

The ultrasound system (either imaging or non-imaging) may be used to measure the amount of microbubbles, their location in space, and their spatial distribution, when generated during the cavitation phase or the heating phase or when the attempt is to reduce the size and amount of the microbubbles. The ultrasound system may use the following flow chart of operations, in order to measure and display or image the microbubbles. This measurement may be used to modify the operation of the system, so as to increase or reduce or shift the amount of microbubbles, or their size.

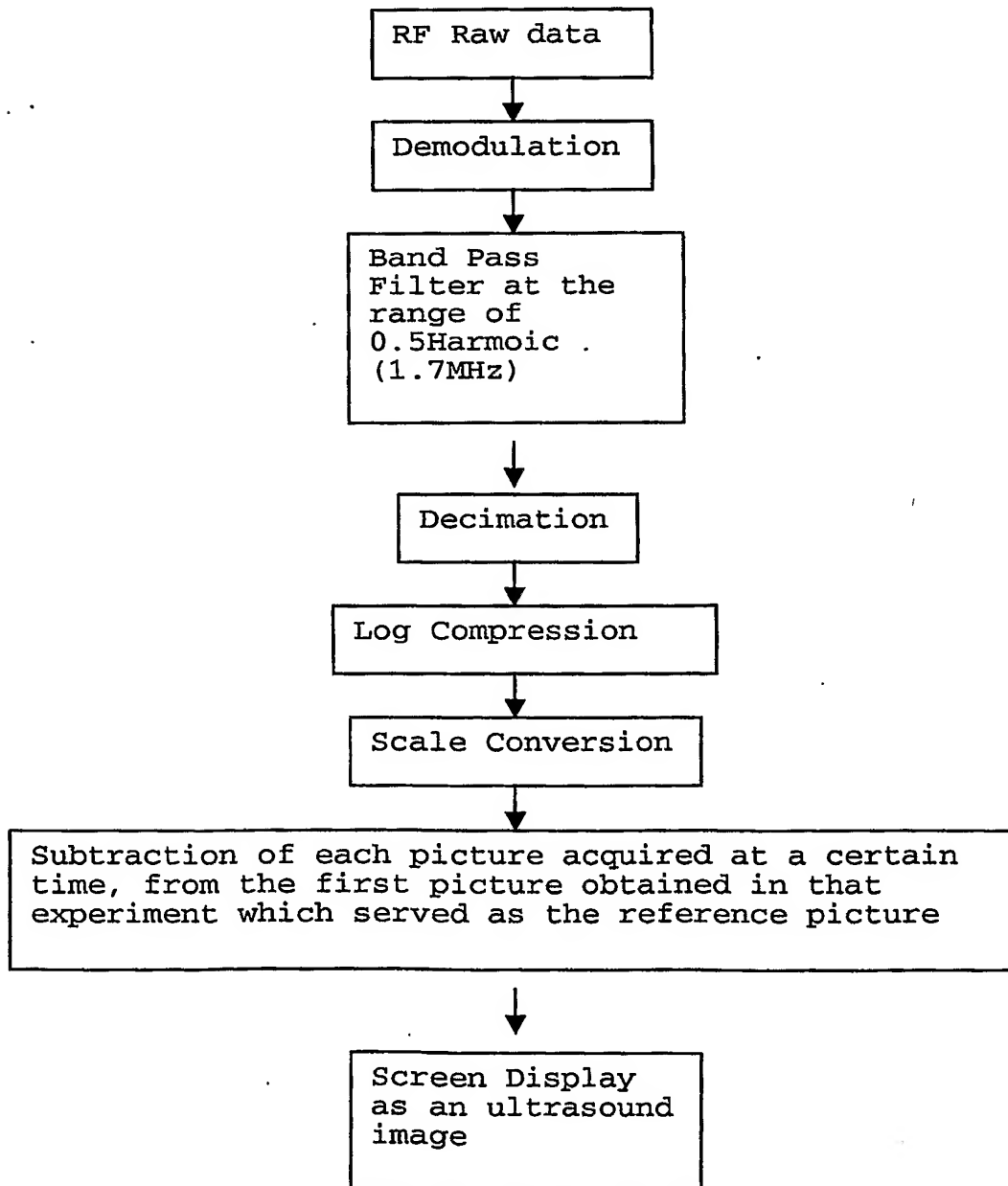


Fig. 11: Flow-chart of the sequence of operations which may be used to measure and display the existence, amount, size, location and spatial distribution of microbubbles generated during one of the stages (or phases) of the procedure. This measurement may be used to modify the operation of the system, so as to increase or reduce or shift the amount of microbubbles, or their size.



The results of this sequence of operations are displayed on a screen, as the example in Fig. 12 demonstrates, where the measurements were made at a specially designed gel phantom, made of gel that does not melt at high temperatures. The gel was prepared with degassed water and spun in a centrifuge to reduce to minimum the amount of dissolved gases and the existence of microbubbles. . After 2 sec of operation of the cavitation phase, no bubbles are noticed. (the bright lines are artifacts of the RF line acquisition). After 16 sec there are already microbubbles, and the amount increase at 30 sec, without translation towards the transducers, as commonly observed. The image at lower right of Fig. 12 was acquired after additional 30 sec of heating when the amount of microbubbles was reduced.

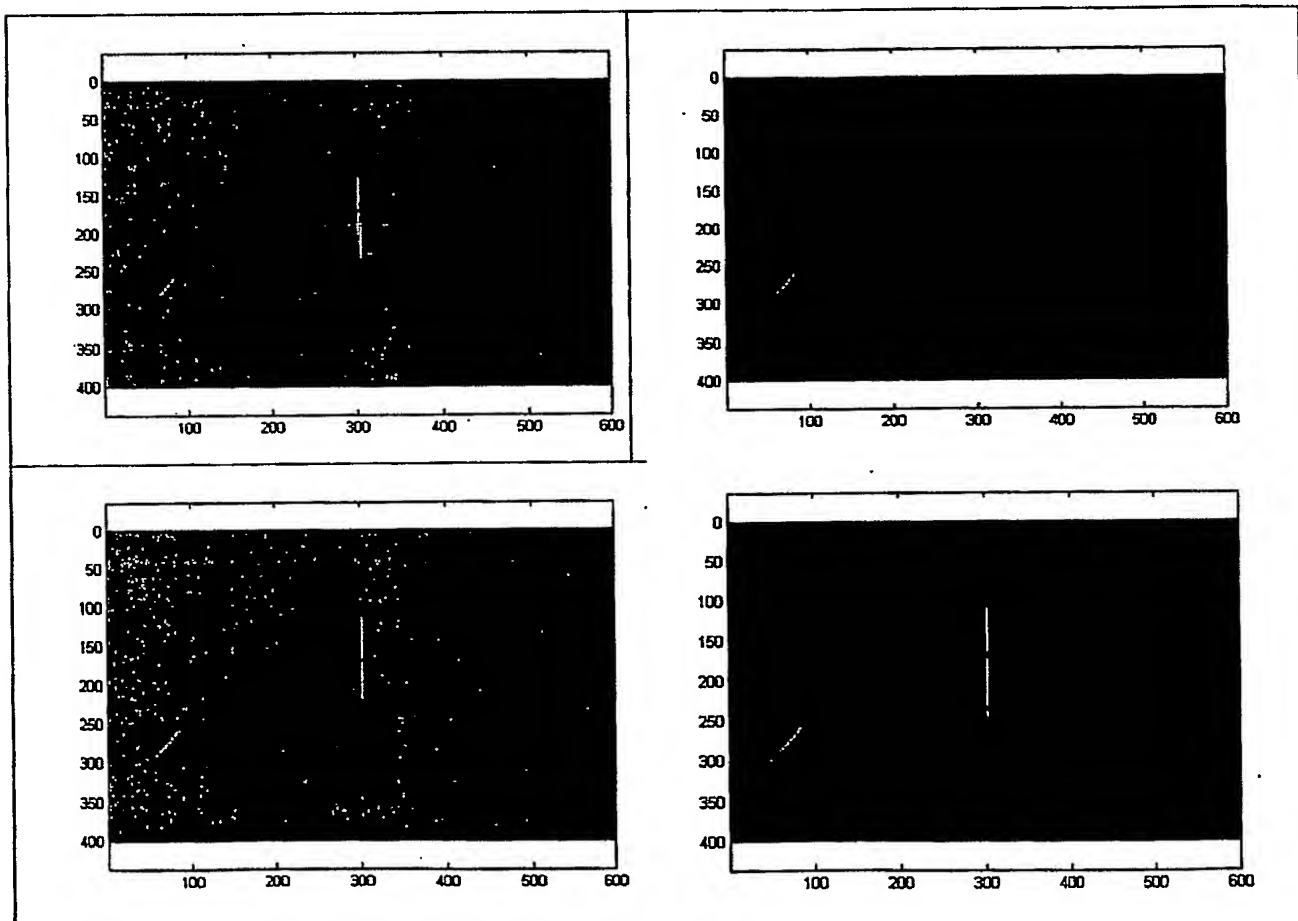


Fig. 12: The images above were acquired after 2 sec (upper left), 16 sec (upper right), 30 sec (lower left) of cavitation production in a gel phantom. The image at lower right was acquired after additional 30 sec of heating when the amount of microbubbles was reduced. .

#### **Results of experiments done with liver tissue (in-vitro):**

The same experiments as above were repeated when the phantom used was excised fresh liver. The liver was kept in saline at room temperature (22 °C), and the array of transducers was aimed at a specific point in the tissue, and the system was operated for the following durations:

30 sec cavitation – 30 sec heating

30 sec cavitation – 60 sec heating

60 sec cavitation – 30 sec heating

60 sec cavitation – 30 sec heating

60 sec heating only

60+60 sec of no cavitation and no heating

The chart in Fig. 13 depicts temperature values ( $^{\circ}\text{C}$ ) after different durations of production of cavitation and heating.

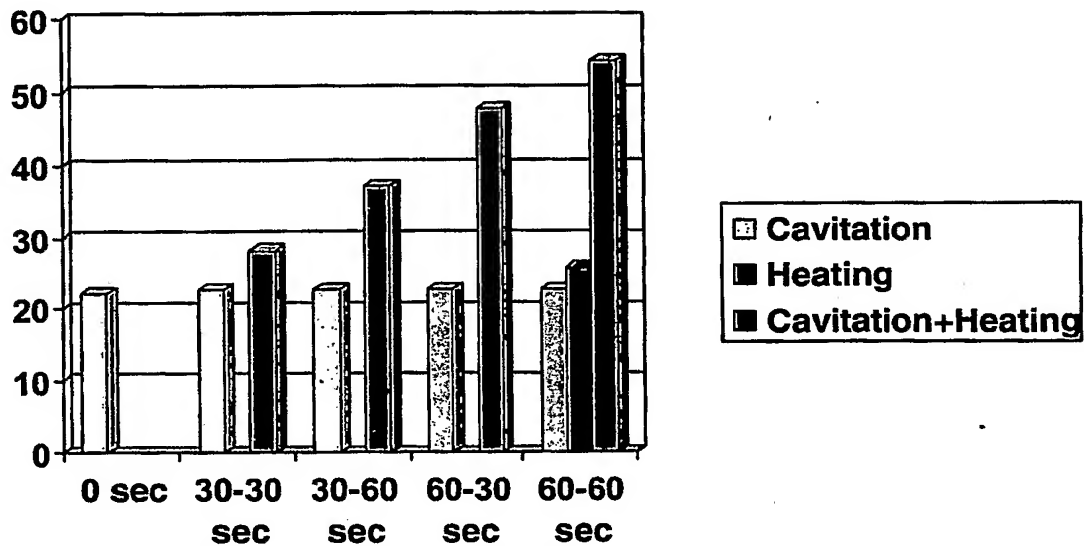


Fig. 13: the chart depicts temperature values ( $^{\circ}\text{C}$ ) after different durations of production of cavitation and heating.

A picture of liver tissue, cut in the middle of the treated region (Fig. 14), taken after production of cavitation+heating, clearly demonstrates a small region that went through denaturation.



Fig. 14: Picture taken after production of cavitation+heating in excised liver tissue, clearly demonstrates in a cut in the middle of the treated region, a small area that went through denaturation.

### Immediate and Future Uses and Applications:

Immediate and future applications and uses of the innovation are ***non-invasively (or minimally invasively)*** produced localized treatment or damage to cells and tissue, either by mechanism of microbubbles oscillations, expulsion or collapse, or by mechanism of hyperthermia based on the existence of the microbubbles (or a combination of both):

- In occlusion of varicose veins by cavitation damage and/or rapid hyperthermia
- In activation of cellular (e.g. endothelial cells) processes in the body, by either localized pressure forces or shear forces, that produce therapeutic responses or damage, for example, localized drug delivery, gene therapy and angiogenesis;
- In therapy of cancerous tissue by cavitation damage and/or rapid hyperthermia, resulting in apoptosis, tissue ablation or necrosis;
- in therapy of cancerous tissue by damage and closure of the supply and drainage vasculature by cavitation, and/or rapid hyperthermia via coagulation of the arteries supplying the tumor;
- in ablation of ectopic foci within the cardiac walls, mainly within the ventricular walls;
- in thrombolysis of clotted or semi-clotted arteries (e.g. coronary arteries, the carotid arteries, cerebral arteries, peripheral arteries etc.)
- in lipolysis or other method of disintegration of fat cells, either by mechanism of microbubbles collapse and/or hyperthermia, resulting in apoptosis and drainage of fat deposits;
- in coagulation of internal bleedings within the body.
- In (non-invasive) surgery of internal tissues and organs, by disintegration of cells along the cut, with possible visualization and control via the generated microbubbles.

These immediate and future applications and uses are operational under guidance and control of ultrasound imaging (or other imaging modality), and can also be operated without such guidance and control, by preset parameters.

## Conclusions:

- Generation of localized damage by cavitation can be produced by the suggested method and system.
- The localized generation of cavitation can also be used for producing efficient hyperthermia, for ablation or coagulation of tissue. This two-stages process is more effective, and includes:
  1. Bubbles creation by cavitation
  2. Thermal heating
- The 2-stage procedure enables visualization of the location of the production of bubbles and allows to decide whether to continue with the treatment, or to change its location
- The verification of the procedure was made by measuring the temperature by thermocouples. Gradual temperature increase at the focal point was observed. Several millimeters away – no temperature changes were observed
- Change in the power level (during cavitation) affect the temperature increase, and the bubbles production. But it has little effect on the duration of the treatment:  
Increased Power level → increased bubbles production and increased temperature
- A disadvantage of using high power level is in producing too many bubbles that are difficult to control
- The results show that a change in heating time affects the temperature increase and the duration of the treatment. But it does not affect the production of bubbles during this stage:  
Increased Heating time → increased temperature and increased treatment time

**Claims:**

1. A method of localized treatment and hyperthermia production by microbubbles and microbubbles-enhanced ultrasound, essentially as described and exemplified herein.
2. A device for localized treatment and hyperthermia production by microbubbles and microbubbles-enhanced ultrasound, essentially as described and exemplified herein.
3. A therapeutic ultrasound essentially as described and exemplified herein.